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09/937,137	09/21/2001	Giammaria Sitar	1271-001	4515

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EXAMINER	
AFREMOVA, VERA	/C/

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/937,137	Sitar
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 21, 2001*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

Claims 1-6 are pending and under examination.

Claim Rejections - 35 USC § 112

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 are indefinite because it is unclear whether the claimed characteristics including pH, osmolarity, concentration of various ions, glucose and lactate are the characteristics of a "non-physiological culture medium" when combined with an "aqueous solution" before addition to a maternal blood or whether the claimed characteristics are the modified maternal blood characteristics after addition of a "non-physiological culture medium" and an aqueous solution. The sequence of combining blood, medium and solution and the characteristics of starting, intermediate and/or final compositions are unclear. The claimed subject matter is uncertain in the light of applications' definitions. For example: on page 5, line 15-24, the characteristics which are presently claimed are said to be the "non-physiological culture medium" characteristics in the absence of "aqueous solution" and maternal blood. However, the same characteristics are said to be the resulting "non-physiological" conditions (page 9, line 4-12) of maternal blood after combining maternal blood with a "tissue culture medium" (page 7, line 7-9) and with an "aqueous solution" (page 9, line 2).

Claims 1 and 3 are also indefinite with regard to concentrations of glucose and lactate. It is unclear what is intended by "d" (claim 1, last line). It is uncertain whether this is a typing error and/or whether liters or deciliters are intended. The issue of glucose and lactate concentration is uncertain as claimed and in the light of applications definitions. For example: on page 5, lines 23-24, concentration is expressed in "mg/dl" but on page 9, line 11, the same amount of glucose is expressed as "mg/l". The source of glucose and lactate is also uncertain what renders that claimed subject matter indefinite and confusing with regard to the sequence of combining blood, medium and solution and the characteristics of starting, intermediate and/or final compositions. For example: it is uncertain whether the claimed amount of glucose and lactate originate from a maternal blood or from a "non-physiological culture medium". The claimed amounts of glucose such as "400-500 mg/dl" are clearly "non-physiological" concentrations and/or conditions. The reference by Guyton [U] teaches that the regular blood or blood plasma glucose amount is about 100 mg/dl (see page 753, col. 2, par. 4 or see page 277, fig. 25-4). Thus, the claimed glucose and lactate appear to derive from a starting "non-physiological culture medium". However, although on the page 5 of specification the "non-physiological culture medium" is said to comprise both glucose and lactate, the medium which is added to maternal blood and which is intended as a medium which would create the "non-physiological" conditions does not comprise either glucose or lactate (table 2, pages 7-9). The issue of glucose and lactate concentration and source is even more confusing because the claimed amounts of glucose are "non-physiological" amount but the claimed amounts of lactate are "physiological" or regular in the light of teaching by Guyton [U]

(see page 277, fig. 25-4). Thus, it appears that they should derive from two different source. Yet, the components of starting, intermediate and/or final compositions in the claimed method are uncertain.

Claim 1 is also indefinite with regard to "tissue culture medium" in the step d). It is unclear as claimed whether this medium is the same or different medium as in step a) because the "non-physiological" and "physiological" characteristics and conditions are uncertain in the method for isolating fetal cells present in maternal blood.

Claims 1 and 2 are rendered indefinite by the use of abbreviated terms "RBCs" and fetal "NRBCs". For example: "RBCs" might be both red blood cells and rare blood cells including fetal cells in maternal blood. "NRBs" might be both nucleated rare/red blood cells and non-nucleated rare/red blood cells. Abbreviation in the first instance of claims should be explained upon with the abbreviation indicated in parentheses. The abbreviations can be used thereafter.

The term "higher density" in claim 1 (line 17) is a relative term which renders the claim indefinite. This term is not clearly defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 1 is rendered indefinite by the phrase "appropriate procedures" (claim 1, line 23) because it is uncertain what is included or excluded by the claim language in the method for isolating fetal cells.

Claim 6 is rendered indefinite by the use of numbers "(1)", "(2)", "(3)" and "(4)". Although the figure drawing of an apparatus in the instant application appears to include the same numbers 1-4, it is uncertain what is their meaning in the claimed method for isolating fetal cells. Thus, claim 6 is indefinite in that it fails to point out what is included or excluded by the claim language in the method for isolating fetal cells. Although it is permitted to refer to a specific figure where there is no practical way to define the invention in words, however it is uncertain whether this is true in the instant application and claims. Applicant is advised to provide clarification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,663,051 [A], US 5,676,849 [B] and US 5,432,054 [C] taken with the reference by Guyton [U].

Claims are directed to a method for isolating fetal cells present in maternal peripheral blood for prenatal genetic investigation wherein the method comprises step of combining a maternal blood sample with a "non-physiological" tissue culture medium and an aqueous solution containing citric acid, sodium citrate and dextran and obtaining a modified maternal

blood, step of transferring the modified maternal blood to a cell separation device and adding a high density liquid containing a red blood cell aggregating agent, step of isolating nucleated cells by subjecting the separation device to centrifugal force, step of washing and resuspending the isolated cells and step of identifying fetal cells. The "non-physiological" culture medium and/or modified blood are characterized by a slightly hypertonic osmolarity of 300-330 mOsm and by particular pH and particular concentrations of sodium, potassium, chloride, calcium, glucose and lactate. Some claims are further drawn to isolating fetal nucleated red blood cells. Some claims are further drawn to the use of a liquid containing a red blood cells aggregating agent such as Ficoll containing preparation. Some claims are further drawn to the use of a liquid in separation device with 1.068 g/ml density.

The cited patents US 5,663,051 [A], US 5,676,849 [B] and US 5,432,054 [C] are relied upon for the disclosure of methods for isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation wherein the methods encompass isolation of fetal nucleated red blood cells by density gradient centrifugation of maternal blood which has been modified by addition of various preparations.

For example: US 5,663,051 [A] teaches a method for isolating nucleated fetal cells present in maternal peripheral blood for prenatal genetic investigation (abstract, col. 21, lines 20-25, example 1) wherein the method comprises step of combining and transferring a maternal blood sample with a "non-physiological" tissue culture medium or "PBS" (col. 35, line 20 or col. 36, line 12) and an aqueous solution or an anticoagulant preparation (col. 35, line 35) in a cell

separation device comprising a high density liquid containing a red blood cell aggregating agent such as Percoll or Ficoll preparations (col. 35, line 42 or col.36, line 13), step of isolating nucleated cells by subjecting the separation device with modified maternal blood to centrifugal force (col. 35, line 41 or col. 36, line 15), step of washing and resuspending the isolated cells (col. 35, line 59 or col. 36, line 21) and step of identifying fetal cells (col. 21, line 57).

The cited patent US 5,663,051 [A] is silent with regard to the contents of an aqueous solution or an anticoagulant preparation. However, US 5,676,849 [B] teaches that the commonly used anticoagulant preparations or the aqueous solutions in the method for isolating nucleated fetal cells from maternal blood (col. 4, lines 10-18) are the acid-citrate-dextrose preparations (col. 6, lines 55-60) as it is encompassed by presently claimed method for the aqueous solution intended to modify the maternal blood prior to centrifugation step. The cited patent US 5,676,849 [B] also teaches combining maternal blood with a "non-physiological" medium comprising chloride, potassium, sodium and other ions (col. 3, lines 18-20 or col. 6, line 67) prior to centrifugation step and the use of high density Ficoll preparation for centrifugal cell separation.

The cited patents US 5,663,051 [A] and US 5,676,849 [B] are lacking the disclosure related to particular "non-physiological" characteristics or conditions including particular concentrations of components in "culture medium" and/or in modified blood. However, US 5,676,849 teaches the use of generic "non-physiological" conditions in order to modify the maternal blood and to induce preferential lysis of maternal red blood cells as the result of

addition of a medium with chloride, potassium, sodium and other ions to maternal blood (col. 3, lines 18-20 or col. 6, line 67). The cited US 5,663,051 [A] also appears to encompasses the use of at least some "non-physiological" conditions by teaching the use of osmolarity of Ficoll preparation such as 320 mOsm (col. 36, line 14) which is within the meaning of "non-physiological" osmolarity conditions as encompassed by the presently claimed method.

Moreover, the patent US 5,432,054 [C] clearly teaches the use of "non-physiological" hypertonic conditions for modifying a maternal blood prior to centrifugation in the method for isolating nucleated red blood cells from maternal blood (see abstract or col. 8, lines 1-14). The cited patent US 5,432,054 [C] also suggests the use of "PBS" solution as a "non-physiological" hypertonic medium (col. 8, line 13) which is taught in the method of US 5,663,051 [A] as explained above. The cited patent US 5,432,054 [C] also teaches the use of a liquid in separation device with density of 1.065 g/ml (col. 12, table 2) or about 1.068 g/ml for centrifugation of modified maternal blood as encompassed by the presently claimed method.

The reference by Guyton [U] is relied upon to demonstrate regular or "physiological" conditions/characteristics of blood such as osmolarity, pH and concentrations of sodium, potassium, chloride, calcium, glucose and lactate (page 277, table 25-2 and figure 25-4; page 331, col. 1, par. 4; page 752, col. 2, par. 4).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice a method for isolating fetal cells present in maternal peripheral blood for prenatal genetic investigation wherein the method encompasses isolation of

fetal nucleated red blood cells by density gradient centrifugation of maternal blood modified by addition of various preparations as taught by the cited patents US 5,663,051 [A], US 5,676,849 [B] and US 5,432,054 [C] with a reasonable expectation of success in isolating fetal nucleated red blood cells as demonstrated by the cited patents. The concept of isolating fetal cells from maternal blood is substantially similar, if not identical, to the concept of the presently claimed method which is also based on a density gradient centrifugation isolation of fetal nucleated red blood cells from modified maternal blood. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. Although the cited patents are lacking the particular disclosure about the final characteristics of modified maternal blood subjected to centrifugation, the claimed invention is uncertain with regard to either starting, intermediate or final characteristics of maternal blood and additional media/solutions. Moreover, the cited patent US 5,432,054 [C] teaches the use of "non-physiological" hypertonic medium/solution for modifying a maternal blood prior to centrifugal cell separation. Thus, one of skill on the art would have been motivated to use solutions with "non-physiological" osmolarity which is above 300 mOsm (see Guyton, table 25-2) as encompassed by the present invention for the expected benefit in maximizing amounts of isolated fetal cells present in maternal peripheral blood intended for prenatal genetic investigations. The "non-physiological" characteristics or conditions as related to concentration of at least lactate, glucose, calcium, chloride and potassium as claimed and/or as disclosed by applicant appear to be within ranges of regular or physiologically acceptable blood conditions as demonstrated by Guyton. Although pH and

amounts of sodium as claimed and as disclosed appear to be outside the ranges of regular or physiologically acceptable blood conditions as demonstrated by Guyton, the cited patents teach the addition of acid-citrate-dextran solution {US 5,676,849} and/or the addition of sodium salts {US 5,432,054} to maternal blood for modifications prior to centrifugal cell separation. Therefore, it is reasonably to expect that the addition of acids and of sodium salts to the maternal blood, which is taught and/or suggested by the cited prior art, would modify the maternal blood and it would decrease pH value and increase sodium amounts comparatively to the starting maternal blood in the methods of the cited patents at least to some extend as encompassed by the presently claimed "non-physiological" conditions. Thus, the claimed subject matter fails to patentably distinguish over the state art as represented be the cited references.

Therefore, the claims are properly rejected under 35 USC § 103.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,663,051 [A], US 5,676,849 [B] and US 5,432,054 [C] taken with the reference by Guyton [U] as applied to claims 1-5 above, and further in view of US 4,424,132 [D], GB 2-75376 [N] and FR 77 08053 [O].

Claims 1-5 as explained above. Claim 6 is further drawn to the use of a particular cell separation device or apparatus in a method for isolating fetal cells present in maternal peripheral blood for prenatal genetic investigation.

The cited patents US 5,663,051 [A], US 5,676,849 [B] and US 5,432,054 [C] are relied upon as explained above for the disclosure of methods for isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation wherein the methods encompass isolation of fetal nucleated red blood cells by density gradient centrifugation of modified maternal blood in various cell separation devices. Although the devices of the cited patents might not contain elongated conical chambers with several attached channels identical to the presently claimed device, the methods of the cited patents resulted in successful separation of fetal cells. Thus, there is a reasonably believe that the cell separation devices of the cited patents are suitable and appropriate in the methods for isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation.

Additional references US 4,424,132 [D], GB 2-75376 [N] and FR 77 08053 [O] are relied upon to demonstrate a large variety of cell separation devices available in the prior art and suitable for cell separation in the present invention directed to a method for isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use a large variety of cell separation devices suitable for separating blood cells including isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation as demonstrated by the cited references. The cited references are in the same field of endeavor and seek to solve the same problems as the instant application and claims such as blood cell separation, and one of skill in the art is free to select

devices available in the prior art. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. Moreover, the devices disclosed by the cited patents US 4,424,132 [D], GB 2-75376 [N] and FR 77 08053 [O] are admitted by applicant as suitable in the presently claimed invention (specification page 6, par. 3). Thus, whatever differences might exist between various cell separation devices of the prior art and the particular device of the present invention, the claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

Art Unit 1651 VERA AFREMOVA

March 14, 2003. PATENT EXAMINER